

Production of ^{99m}Tc and ^{99}Mo at PXIE

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Abstract

The isotope ^{99m}Tc is used extensively around the world for diagnostic medical imaging. Possible limitations in the supply of ^{99}Mo , a parent isotope of ^{99m}Tc , are spurring alternative production methods of both isotopes. This note describes the potential for production of ^{99m}Tc and ^{99}Mo at the proposed PXIE facility at Fermilab.

Introduction

The isotope technetium-99m (^{99m}Tc) is used for over 30 million diagnostic medical imaging scans every year around the world [1]. ^{99m}Tc decays to the technetium-99 ground state (^{99g}Tc) with a half-life of 6 hours by emitting a 140 keV photon that is detected by the imaging devices. Since the ^{99m}Tc half-life is short, it must be produced within a reasonably short time or distance from where it is used. Fortunately, molybdenum-99 (^{99}Mo) decays predominantly to ^{99m}Tc with a half-life of 66 hours. Medical centers or commercial radiopharmaceutical distributors purchase ^{99}Mo - ^{99m}Tc generators from which ^{99m}Tc (and necessarily ^{99g}Tc) can be extracted periodically in a simple chemical process as it accumulates from the parent ^{99}Mo decays. The ^{99}Tc is then bound into the pharmaceutical of choice for the imaging procedure.

The predominant source of ^{99}Mo is as a fission product of highly enriched ^{235}U (HEU). However, there are only five reactors worldwide (none in the US) that provide essentially the entire supply of ^{99}Mo – see Table 1. As of 2010, the weekly global demand of ^{99}Mo was ~50,000 Ci (activity

Name	Location	Age [years]	Thermal Power [MW]	Thermal neutron flux [10^{14} n/cm ² /s]	Typical ⁹⁹ Mo production share
NRU	Canada	55	135	4.0	40%
HFR	Netherlands	51	45	2.7	30%
BR-2	Belgium	51	100	10.0	10-15%
Safari-1	South Africa	47	20	2.4	10-15%
OSIRIS	France	46	70	1.7	5-8%

Table 1: (Adapted from [1]) The nuclear reactors used for large scale production of ⁹⁹Mo via fission of highly enriched ²³⁵U.

before processing material into generators) [1], and expected to grow with the 3-5% per year increase of ^{99m}Tc use. Several lower power reactors do provide smaller scale ⁹⁹Mo production for regional use. Any operational interruption, planned or not, to one of the large reactors can disrupt the supply chain significantly. The NRU and OSIRIS reactors will likely cease operation during the next decade, prompting efforts to create new, reliable sources of ⁹⁹Mo. In addition, security issues with HEU are forcing the investigation and use of low enriched uranium (LEU) which has correspondingly lower production rate. Several such LEU reactors should be coming online over the next several years.

Various accelerator-based schemes for ⁹⁹Mo production and direct production of ^{99m}Tc are being studied [1], [2], [3]. For proton beam energies close to 25 MeV, like that proposed for PXIE, ^{99m}Tc can be produced directly via the reaction $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$. ⁹⁹Mo can also be produced via $^{100}\text{Mo}(p,pn)^{99}\text{Mo}$, but as will be shown later, the ⁹⁹Mo decays provide only a small additional contribution to ^{99m}Tc production. On a related topic, a neutron source driven by a 1 mA proton beam at 1 GeV, such as that at Stage 1 of Project X, could produce considerable quantities of ⁹⁹Mo via $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$.

This note examines the production of ^{99m}Tc and ⁹⁹Mo using a high intensity proton beam like that proposed for the PXIE facility at Fermilab.

Production

The most straightforward processes for accelerator-based production of ^{99m}Tc and ^{99}Mo are the nuclear reactions $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ and $^{100}\text{Mo}(p,pn)^{99}\text{Mo}$. There are seven naturally occurring isotopes of molybdenum with abundances shown in Table 2. Since ^{100}Mo has a natural abundance of only $\sim 10\%$, using a target enriched with ^{100}Mo is necessary to boost the production rates of the desired isotopes and improving radionuclidic purity by minimizing production of other unwanted isotopes. ^{100}Mo is available with $>97\%$ enrichment from various sources. In addition, techniques for recycling leftover ^{100}Mo from irradiated target material are being pursued.

Isotope	Abundance
92	14.80%
94	9.25%
95	15.92%
96	16.68%
97	9.55%
98	24.13%
100	9.63%

Table 2: Abundances of naturally occurring isotopes of molybdenum [4].

Equation 1 is the production rate P for an isotope with production cross section $\sigma(E)$ by a proton beam of current I_B incident on a target with atomic weight A . The cross section is convoluted with the beam energy loss through the material (essentially all due to ionization of target atoms at these energies) between the incident beam energy E_1 and the (average) energy of the beam E_2 after traversing the target.

$$P = \frac{N_A I_B}{A} \int_{E_1}^{E_2} \frac{\sigma(E)}{\frac{1}{\rho} \frac{dE}{dx}(E)} dE \quad (1)$$

When producing radioactive isotopes, the total number of those atoms present at time t must include a term accounting for their decay:

$$N(t) = \frac{P}{\lambda} (1 - e^{-\lambda t}) \quad (2)$$

where $\lambda = (\ln 2) / t_{1/2}$ is the decay constant of the radioactive isotope of interest. The number of radioactive atoms will eventually saturate when the instantaneous decay rate matches the production rate; Figure 1 illustrates this saturation effect. Typically, an isotope production bombardment run will not exceed three half-lives. The Appendix contains additional formulas on the indirect production of stable and radioactive isotopes.

As previously mentioned, it is beneficial to have a target enriched in ^{100}Mo . To estimate the $^{99\text{m}}\text{Tc}$ production rate, I assume a 100% pure ^{100}Mo target. I neglect the engineering challenges in designing and operating such a target to withstand the tens of kilowatts of beam power that will be available at PXIE. (A molybdenum oxide may be a more suitable target material.) The ionization energy loss $1/\rho \, dE/dx$ for protons on ^{100}Mo is shown in Figure 2. Using a density of $10.7 \, \text{g/cm}^3$ for ^{100}Mo (scaled from density of natural Mo), the energy loss at 24 MeV is approximately 13 MeV/mm,

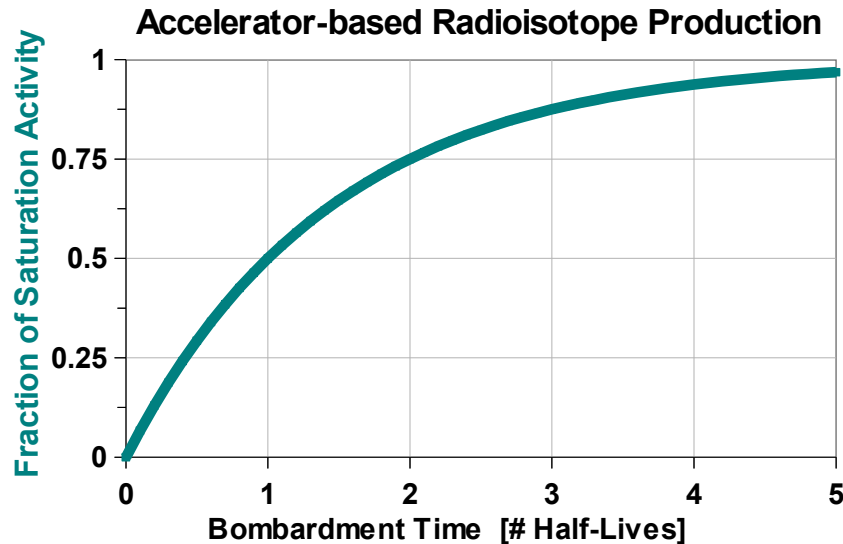


Figure 1: Fraction of saturation activity as a function of time (in half-lives) for production of a radioactive isotope by bombarding a target with an accelerated beam of particles.

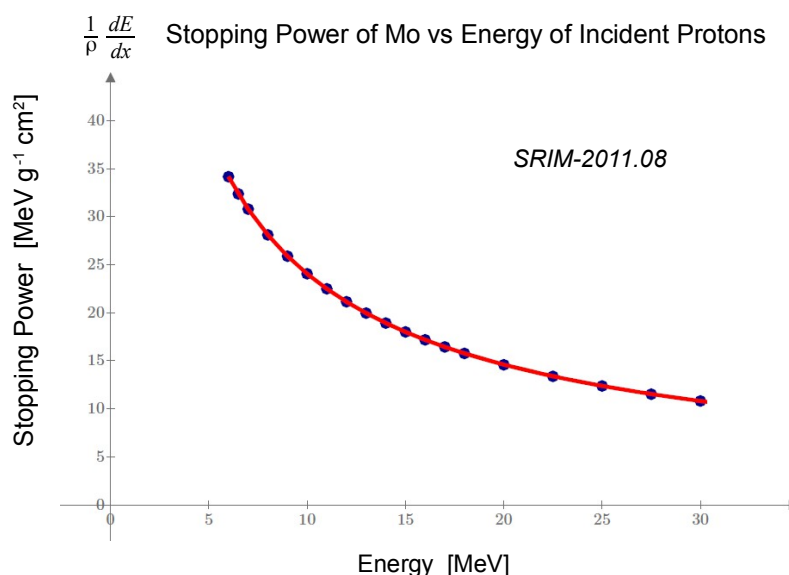


Figure 2: Stopping power of molybdenum for incident protons.

and the thickness needed to degrade the beam energy from 24 MeV to 10 MeV is only $\approx 900 \mu\text{m}$. The choice of those particular energies will be explained later.

There have been many measurements of the $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ cross section, as shown in Figure 3. There is up to a factor 2 of spread among the data at the peak near 17 MeV. It is a subtle task to separate the several possible production paths that can yield $^{99\text{m}}\text{Tc}$ in those experiments, and there are also other isotopes present that emit gamma rays with energies close to the $^{99\text{m}}\text{Tc}$ 140 keV photon. Some measurements are suspected to be faulty, but the recent measurement performed by Gagnon et al. [3] seems to be robust, and we use those results for the $^{99\text{m}}\text{Tc}$ estimates in this note.

An important consideration for accelerator-based production of $^{99\text{m}}\text{Tc}$ is the co-production of ground state technetium ($^{99\text{g}}\text{Tc}$) during the bombardment. Since $^{99\text{g}}\text{Tc}$ is chemically identical to $^{99\text{m}}\text{Tc}$, there is no way to separate the medically-useful radioactive (hot) $^{99\text{m}}\text{Tc}$ from the ground state (cold) $^{99\text{g}}\text{Tc}$ atoms. During the synthesis of the radiopharmaceutical tracer that will be administered to a patient, both the hot and cold atoms are incorporated equally well. Once injected into the body, the tracer molecules with and without the radioisotope bind competitively to the same target locations. Consequently, it is desired to have as high a fraction of tracer molecules labeled radioactively as

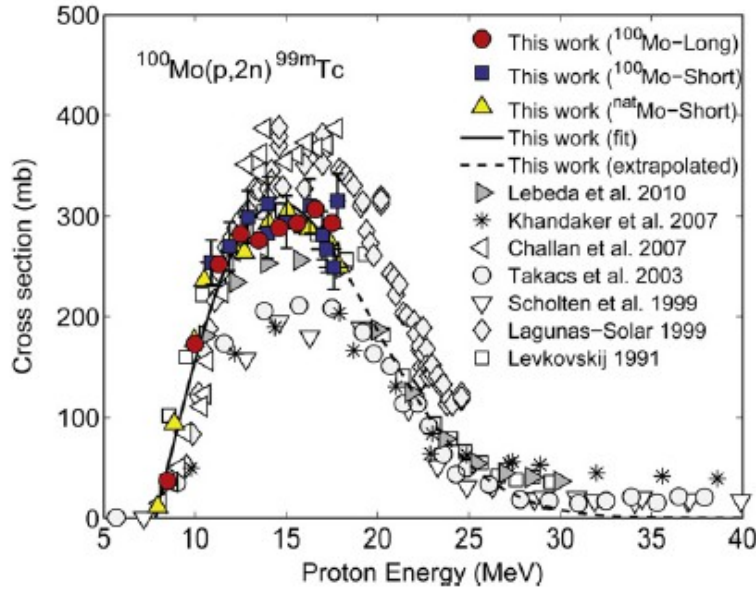


Figure 3: Summary of $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ cross section measurements taken from [3].

possible. In the parlance of nuclear medicine, it is better to have a large *specific activity* – amount of radioactivity per mass of a compound, sometimes specified in units of mCi/ μmol or Ci/g.

The cross section of $^{100}\text{Mo}(p,2n)^{99\text{g}}\text{Tc}$ was first reported by Gagnon et al. in 2011 [3]. That data along with their $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ data is shown in Figure 4. The solid and dashed curves represent fits and extrapolations of their cross section data to the functional form $\sigma(E) = A(E - E_0) \exp \frac{-(E - E_0)^2}{2s^2}$ where A , E_0 , and s are the fit parameters whose values are given in Table 3. Clearly, the cross section for $^{99\text{g}}\text{Tc}$ production is higher than $^{99\text{m}}\text{Tc}$ and so it is produced much more copiously than $^{99\text{m}}\text{Tc}$. Nevertheless, the resulting fraction of $^{99\text{m}}\text{Tc}$ under various beam energy and irradiation time scenarios, 19%-31%, is similar to standard $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators when eluted (Tc extracted from the generator) every 24 hours [3]. These results are rather encouraging since it may be possible to employ standard tracer synthesis methods using the accelerator-produced $^{99\text{m}}\text{Tc}$.

A nominal proton energy range for $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ production can be chosen as 24 MeV to 10 MeV. The 24 MeV incident energy is greater than the energy of the peak cross section (see Figure 4), so that the beam energy passes through the range with highest cross section as it loses energy by ionization losses in the target material. The cross section only continues to decrease beyond 24 MeV,

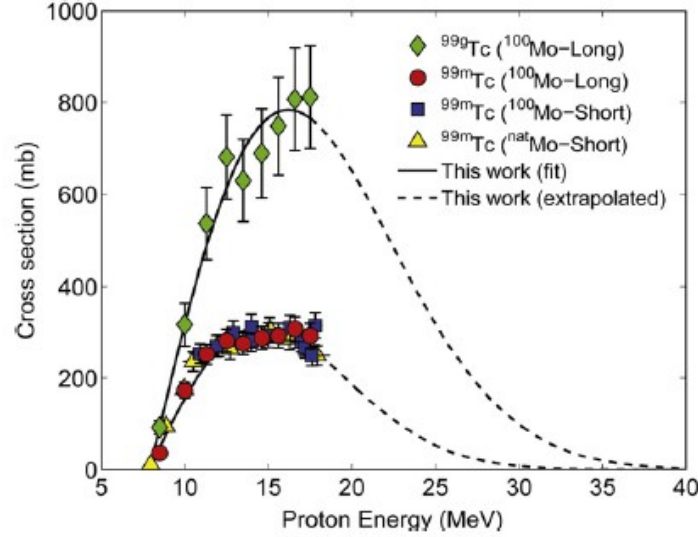


Figure 4: $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ and $^{100}\text{Mo}(p,2n)^{99\text{g}}\text{Tc}$ cross section measurements and extrapolations taken from [3]. The solid lines represent a fit to the data points, while the dashed lines are extrapolations of the fitted functions to higher beam energies.

so there is little benefit to a higher energy. Moreover, one can limit production of other unwanted isotopes by staying below their threshold energy. The lower 10 MeV value is chosen to be slightly above the threshold of ≈ 8.5 MeV. A thicker target would yield only negligibly more $^{99\text{m}}\text{Tc}$ at the expense of absorbing additional beam power. For a thickness corresponding to 14 MeV energy loss, a target would need to absorb 14 kW of beam power at 1 mA current – roughly half of the nominal PXIE beam power. After passing through such a production target, the remaining degraded beam would need to be stopped by a downstream dump. A beam energy of 24 MeV is well matched to the nominal PXIE design of 25 MeV. Even if PXIE were to achieve 30 MeV, an energy degrader could be placed in front of the target.

	A [mb/MeV]	E_0 [MeV]	s [MeV]
$^{99\text{g}}\text{Tc}$	155.70	7.901	8.299
$^{99\text{m}}\text{Tc}$	75.83	7.846	6.801

Table 3: The values of the $^{99\text{g}}\text{Tc}$ and $^{99\text{m}}\text{Tc}$ production cross section fit parameters from [3].

In addition to the direct production of $^{99\text{m}}\text{Tc}$, there are a few indirect mechanisms contributing to

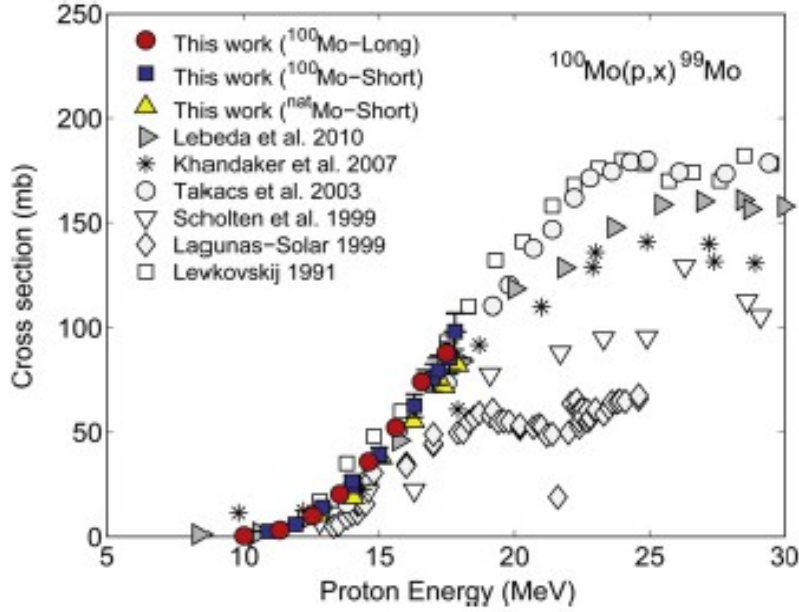


Figure 5: Summary of $^{100}\text{Mo}(p,x)^{99}\text{Mo}$ cross section measurements taken from [3].

$^{99\text{m}}\text{Tc}$ via decay of ^{99}Mo produced directly and indirectly during irradiation of ^{100}Mo [3]. I include $^{100}\text{Mo}(p,pn)^{99}\text{Mo} \rightarrow ^{99\text{m}}\text{Tc}$, but its contribution will be shown to be small compared to direct production. Figure 5 shows a summary of cross section measurements for the $^{100}\text{Mo}(p,x)^{99}\text{Mo}$ process. There is a significant spread in the measurements, especially above 20 MeV, so a simple, ad hoc approximation is used for ^{99}Mo production. This approximation, shown in Figure 6 along with the $^{99\text{g}}\text{Tc}$ and $^{99\text{m}}\text{Tc}$ cross section models, has a threshold of 10 MeV and rises linearly to 22 MeV where it reaches at plateau of 150 mb.

Results

The population (activity) of $^{99\text{m}}\text{Tc}$, $^{99\text{g}}\text{Tc}$ and ^{99}Mo isotopes as a function of time were calculated for bombarding a pure ^{100}Mo target with a 1 mA proton beam at 24 MeV for up to 15 hours; the target does not fully stop the beam, its thickness is such to degrade the beam energy to 10 MeV. Figure 7 illustrates production via the direct channels $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$, $^{100}\text{Mo}(p,2n)^{99\text{g}}\text{Tc}$, and $^{100}\text{Mo}(p,pn)^{99}\text{Mo}$. Clearly, $^{99\text{g}}\text{Tc}$ is produced more copiously than $^{99\text{m}}\text{Tc}$ and ^{99}Mo . The saturation of $^{99\text{m}}\text{Tc}$ is also evident at the longer bombardment durations. Figure 8 shows production of $^{99\text{m}}\text{Tc}$ and $^{99\text{g}}\text{Tc}$ via indirect channels.

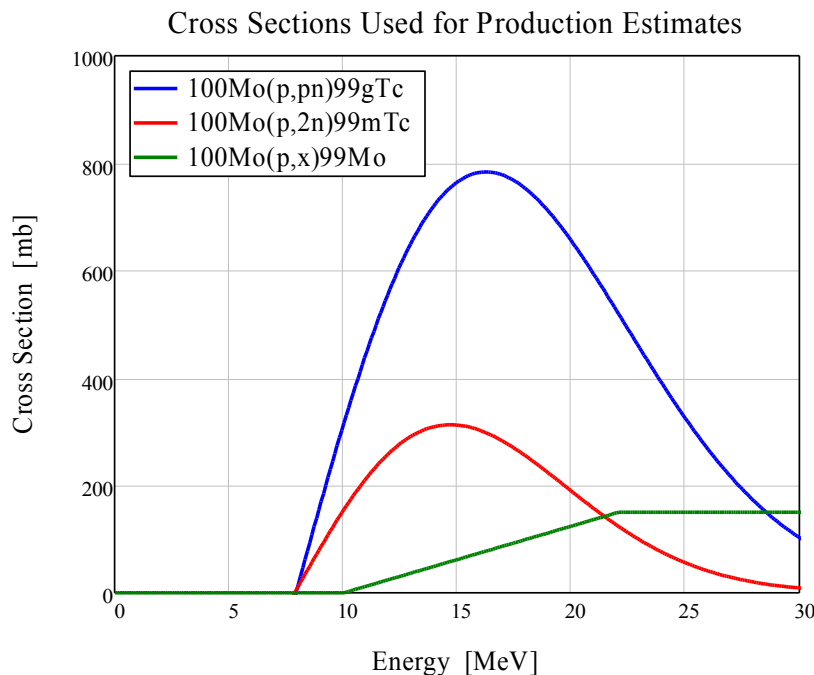


Figure 6: Cross sections used for estimating production of ^{99g}Tc , ^{99m}Tc , and ^{99}Mo .

When comparing Figure 7 and Figure 8, one sees that the production of ^{99m}Tc from ^{99}Mo decay is nearly 2 orders of magnitude lower than the direct production. The generation of ^{99g}Tc from decays of directly-produced ^{99m}Tc is roughly an order of magnitude lower than the direct production; ^{99g}Tc generation via ^{99}Mo decays is still another factor of 100 lower. Figure 9 depicts the combined production from both direct and indirect mechanisms; since the direct channels are so much more prodigious, there is little difference between Figure 7 and Figure 9.

Figure 10 shows the fraction $^{99m}\text{Tc} / (^{99m}\text{Tc} + ^{99g}\text{Tc})$ as a function of bombardment time. Recall this quantity is important for medical imaging since the radioactive and ground state Tc atoms can not be separated chemically, so one would like as much of the “hot” isotope administered to the patient in a given dose of tracer compound. The ^{99m}Tc fraction is nearly 25% for short bombardment times and falls gradually to 15% at roughly 11 hours. Any optimization of bombardment time and beam current would need to incorporate extraction of the ^{99}Tc and synthesis of the given radiotracer compound, activity demand, and potential delivery times to imaging sites. Such a problem is beyond the scope of this note.

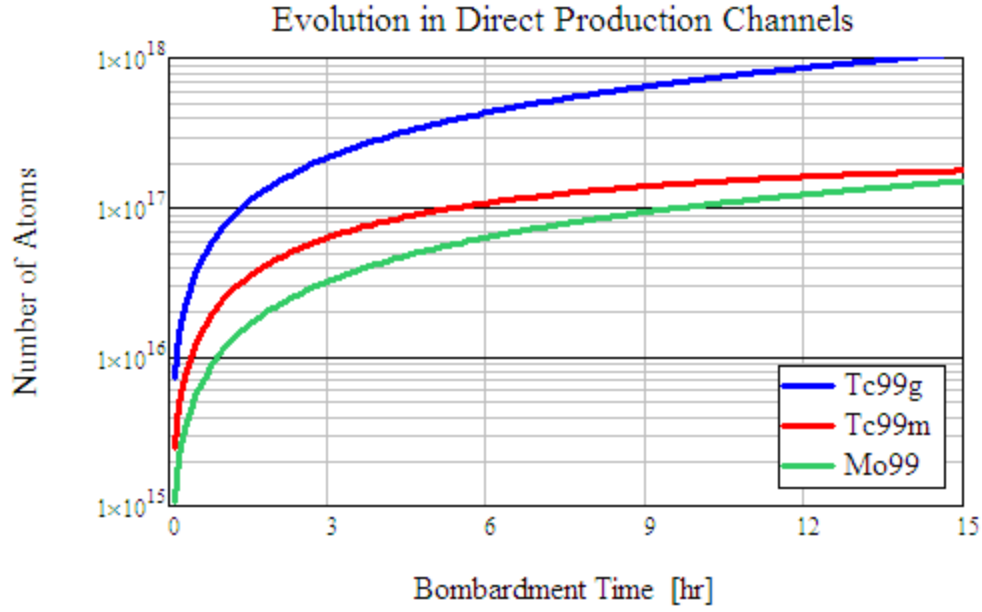


Figure 7: Production of ^{99g}Tc , ^{99m}Tc , and ^{99}Mo versus time via direct channels $^{100}\text{Mo}(p,2n)^{99}\text{Tc}$ and $^{100}\text{Mo}(p,pn)^{99}\text{Mo}$ with 1 mA beam on a 100% ^{100}Mo target from 24 MeV \rightarrow 10 MeV.

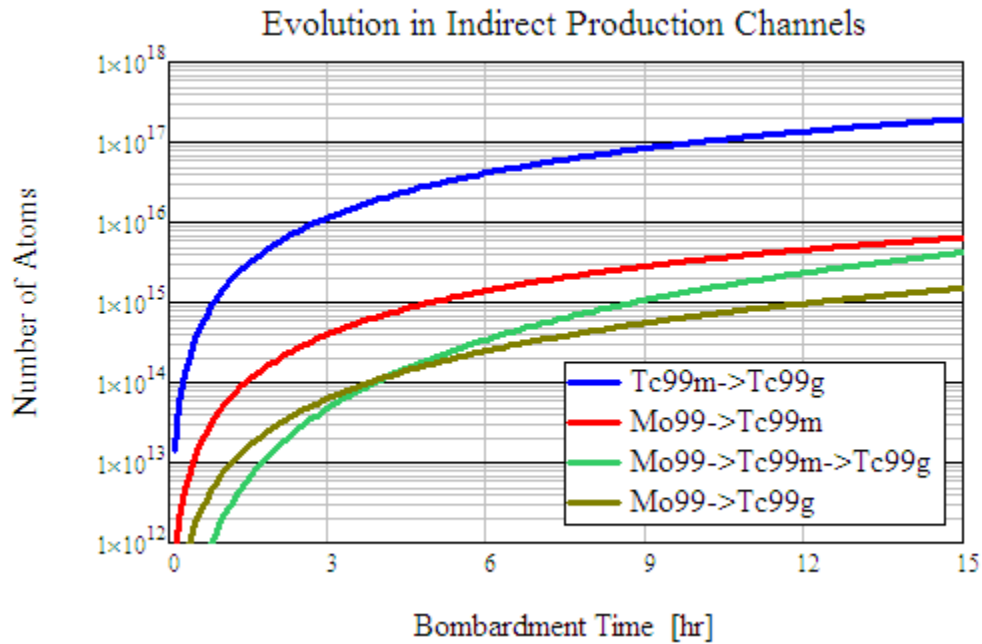


Figure 8: Indirect production of ^{99g}Tc and ^{99m}Tc versus time from decays of directly produced ^{99m}Tc and ^{99}Mo with 1 mA beam on a 100% ^{100}Mo target from 24 MeV \rightarrow 10 MeV.

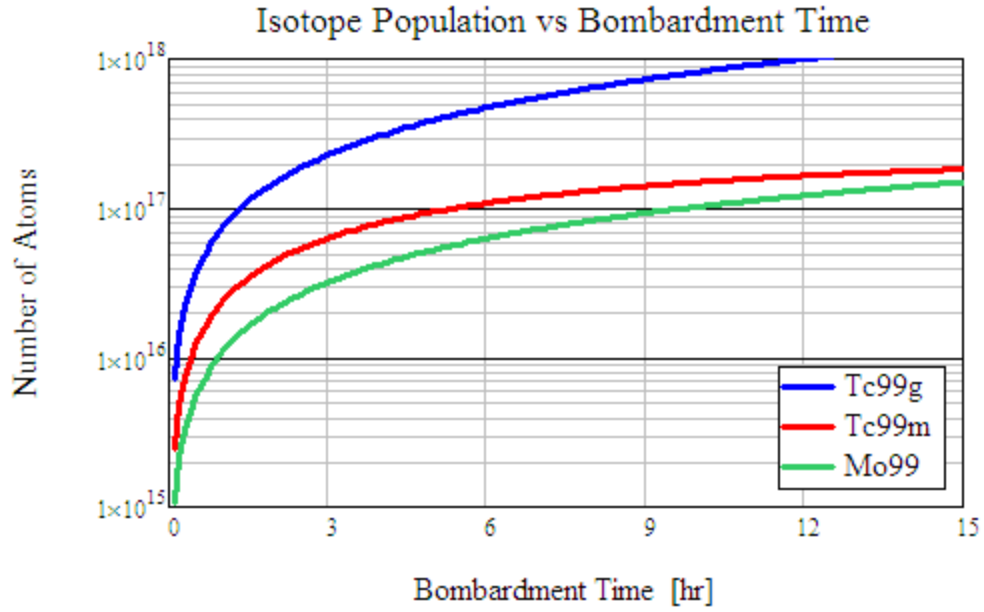


Figure 9: Combined production of ^{99g}Tc , ^{99m}Tc , and ^{90}Mo versus time via direct and indirect channels with 1 mA proton beam on a 100% ^{100}Mo target from 24 MeV \rightarrow 10 MeV.

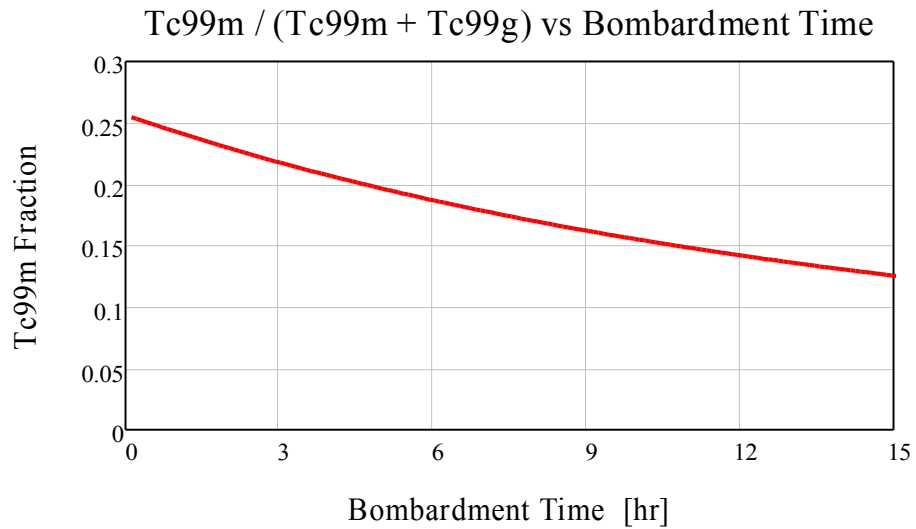


Figure 10: Ratio of ^{99m}Tc to ($^{99m}\text{Tc} + ^{99g}\text{Tc}$) versus time for direct and indirect production from 1 mA proton beam on a 100% ^{100}Mo target from 24 MeV \rightarrow 10 MeV.

Table 4 summarizes production of ^{99m}Tc for irradiation durations of 1 hour, 3 hours and 6 hours. The quantities produced are quite substantial, while the ^{99m}Tc fraction remains similar to what is available from standard $^{99}\text{Mo}/^{99m}\text{Tc}$ generator technology. Such quantities from a single source could supply the ^{99m}Tc needs of a large population region of several million people [5]. Table 5 summarizes the ^{99}Mo production for similar bombardment scenarios as in Table 4; although not negligible, even a very long bombardment at 1 mA does not yield enough ^{99}Mo to serve as a single source for a regional distribution.

Bombardment Duration [hr]	^{99m}Tc in Sample			$^{99m}\text{Tc} /$ ($^{99m}\text{Tc} + ^{99g}\text{Tc}$)
	N	Activity [Ci]	Activity [TBq]	Ratio [%]
1	2.3×10^{16}	20	0.75	24
3	6.3×10^{16}	54	2.0	22
6	1.1×10^{17}	93	3.4	19

Table 4: Amount of ^{99m}Tc (number of atoms and corresponding activity) and fraction of ^{99m}Tc to total ^{99}Tc present after bombarding a pure ^{100}Mo target with 1 mA protons at 24 MeV. The target thickness degrades the beam energy only to 10 MeV. (1 TBq = 10^{12} decays / sec)

Bombardment Duration [hr]	^{99}Mo in Sample		
	N	Activity [Ci]	Activity [GBq]
1	1.1×10^{16}	0.85	31
3	3.2×10^{16}	2.5	93
6	6.3×10^{16}	4.9	183
150	8.1×10^{17}	64	2400

Table 5: Amount of ^{99}Mo (number of atoms and corresponding activity) and fraction of ^{99}Mo to total ^{99}Mo present after bombarding a pure ^{100}Mo target with 1 mA protons at 24 MeV. The target thickness degrades the beam energy only to 10 MeV. (1 GBq = 10^9 decays / sec)

Summary

The isotope ^{99m}Tc is the most widely used isotope for diagnostic medical imaging around the world. The growing demand for ^{99m}Tc and the unreliable future supply of its parent isotope ^{99}Mo are driving investigation into alternative methods of producing those isotopes. Both isotopes can be produced by bombarding protons onto a target containing ^{100}Mo . The proposed PXIE facility at Fermilab has very favorable beam energy and current (1 mA protons at 25 MeV) for producing significant amounts of ^{99m}Tc that could support the medical imaging needs for a large population center. A 3 hour long bombardment of 1 mA protons at 24 MeV onto a pure ^{100}Mo target could produce up to 54 Ci (2 TBq) of ^{99m}Tc with a fraction of $^{99m}\text{Tc} / (^{99m}\text{Tc} + ^{99g}\text{Tc})$ similar to existing ^{99}Mo - ^{99m}Tc generator technology in use for medical imaging. Under the same irradiation scenario, 2.5 Ci (93 GBq) of ^{99}Mo could be produced. Additional development is needed for designing a target capable of withstanding tens of kilowatts of incident beam power.

Appendix

Here we present the analytic formulas used to calculate the production of the isotopes of interest as a function of time. In general, the number of isotopes at time t , $N(t)$, can be found by solving the equation $dN/dt = (\text{production rate}) - (\text{decay rate})$, where the production rate and decay rate terms depend upon the mechanisms for the isotopes of interest.

For direct production by bombardment of target to produce a *stable* isotope 1, as in $^{100}\text{Mo}(p,2n)^{99g}\text{Tc}$, the number of isotope 1 atoms simply increases linearly with time: $N_1(t) = Pt$ where P is the production rate given by (1). If isotope 1 is radioactive and decays to isotope 2, the exponential decay rate term must be included, such that $dN_1/dt = P - \lambda_1 N_1(t)$ where $\lambda_1 = \ln(2)/t_{1/2}$ represents the decay constant of isotope 1 with half-life $t_{1/2}$. Solving for $N_1(t)$ with the initial condition $N_1(0) = 0$ gives $N_1(t) = \frac{P}{\lambda_1}(1 - e^{-\lambda_1 t})$ as shown in (2).

An isotope that is produced indirectly is created in the decay chain of a directly produced radioactive isotope. For a $1 \rightarrow 2$ style production like $^{100}\text{Mo}(p,pn)^{99}\text{Mo} \rightarrow ^{99m}\text{Tc}$, where the decay has a branching fraction f_{12} , the population of a *radioactive* isotope 2 includes a production rate equal to the decay rate of isotope 1 and its own decay rate: $\frac{dN_2}{dt} = \lambda_1 N_1(t) - \lambda_2 N_2(t)$. Using the expression for $N_1(t)$ in the previous paragraph along with the initial conditions $N_1(0) = 0$ and $N_2(0) = 0$, we find:

$$N_2(t) = f_{12} \frac{P}{\lambda_2} \left(1 + \frac{\lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_1 t} - \frac{\lambda_1}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} \right).$$

If isotope 2 is stable, we take the limit of the above expression as $\lambda_2 \rightarrow 0$ to find

$$\lim_{\lambda_2 \rightarrow 0} N_2(t) = f_{12} P \left(t - \frac{1}{\lambda_1} e^{-\lambda_1 t} \right)$$

as the number of *stable* isotope 2 atoms as a function of time.

We can take the indirect production one more step for a $1 \rightarrow 2 \rightarrow 3$ chain such as $^{100}\text{Mo}(p,pn)^{99}\text{Mo} \rightarrow ^{99m}\text{Tc} \rightarrow ^{99g}\text{Tc}$. For a *stable* isotope 3 produced in the isotope 2 decay with branching

fraction f_{23} :

$$N_3(t) = f_{12} f_{23} P \left[t - \frac{\lambda_2}{\lambda_1(\lambda_1 - \lambda_2)} e^{-\lambda_1 t} + \frac{\lambda_1}{\lambda_2(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} - \frac{\lambda_1 + \lambda_2}{\lambda_1 \lambda_2} \right].$$

In general for a chain of radioactive isotopes, the equations $dN_i/dt = \lambda_{i-1} N_{i-1}(t) - \lambda_i N_i(t)$ where the index i represents one generation in the decay chain, describe the number of each generation's isotopes over time. There is a general solution for the $N_i(t)$ called the *Bateman equations* for the condition $N_1(0) = N_0$ and all other $N_i(0) = 0$.

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